6. List of components by name

- Sodium [I-123]iodide
- tBOC-5-IA-$SnMe_3$ [(*S*)-*N*-*t*-butoxycarbonyl-3-(2-azetidinylmethoxy)-5-trimethylstannyl-pyridine]
- Dehydrated alcohol injection, USP
- L-ascorbic acid
- Sterile sodium chloride injection, USP (0.9 % NaCl)

7. Quantitative Composition of Drug

Each dose contains:

[I-123]5-IA	NMT[1] 15		mCi
5-IA †	NMT	0.9	µg
Dehydrated alcohol injection	NMT	800	µL
L-ascorbic acid	NMT	400	µg
0.9 % NaCl	NMT	8	mL

† *Calculations*:

Assuming a dose of 15 mCi and specific activity of >>5,000 mCi/µmol, corresponding to <0.058 µg/mCi, maximum mass dose of carrier = (15 mCi)•(0.058 µg/mCi) = 0.87 µg.

Table 1. Batch Formula Quantity

Component	Per Batch	Per Dose
tBOC-5-IA-$SnMe_3$ precursor	300 µg	§
I-123	10–60 mCi ¶	NMT 15 mCi ¶
Dehydrated alcohol injection	800 µL	NMT 800 µL
L-ascorbic acid	400 µg	NMT 400 µg
0.9% NaCl	8–10 mL	NMT 10 mL

§ Removed during processing

¶ Calculated at time of calibration

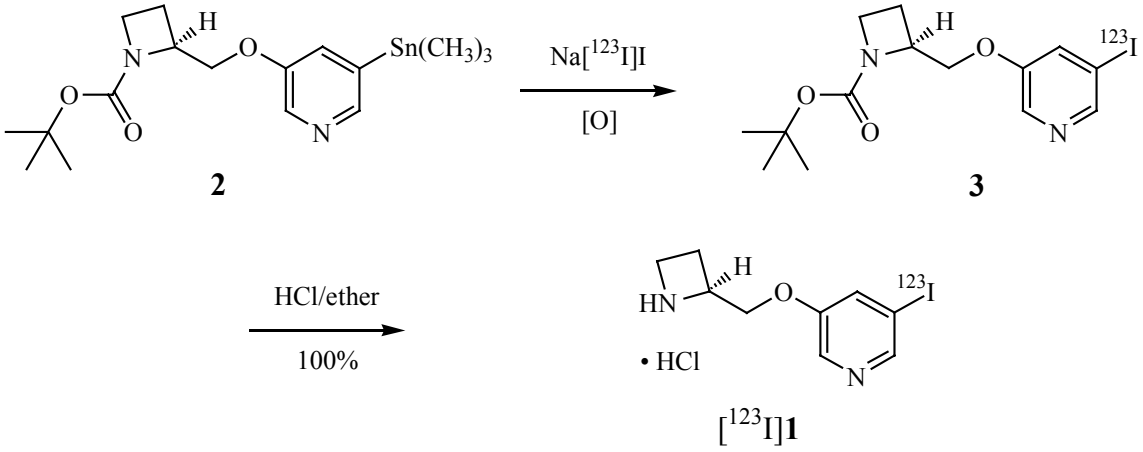
8. Theoretical yield and limits

Theoretical yield is 100% incorporation of radiolabel into the radiolabeled tracer. Actual yields in radiochemical preparation can be expected to be in the range 35-60% (see Table 2, page 4).

9. Description of source and preparation of new drug substance

1 *Abbreviations* NMT, Not More Than; NLT, Not Less Than

*a) [I-123]5-IA [(*S*)-3-(2-azetidinylmethoxy)-5-[I-123]iodopyridine)]*



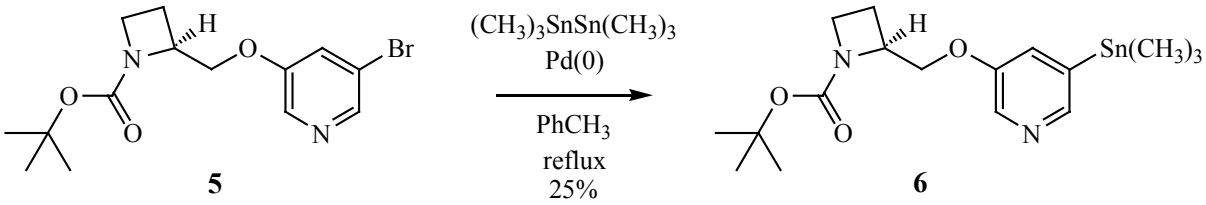
Scheme I. Synthesis of [I-123]5-IA from t-BOC protected trimethylstannyl precursor by iododestannylation followed by deprotection.

The new drug substance is a sodium chloride (0.9%) solution of no-carrier-added [I-123]5-IA [(*S*)-3-(2-azetidinylmethoxy)-5-[I-123]iodopyridine)]. It is prepared (Zoghbi et al 2001) by a slight modification of the iododestannylation reaction on the protected stannyl precursor **2** (tBOC-5-IA-$SnMe_3$; Scheme I) with Na[I-123]I in the presence of chloramine-T (*N*-chloro-*p*-toluenesulfonamide sodium salt) as an oxidizing agent to generate electrophilic iodine or alternatively using the oxidizing agent peracetic acid. After purification of the intermediate I-123 labeled t-BOC-protected 5-IA (**3**) via solid phase extraction (SPE) using a "C_{18} Sep Pak", the t-BOC protecting group is removed quantitatively with hydrogen chloride in ether. After removal of the solvent and HCl(*g*) by evaporation, the residue is further purified by high pressure liquid chromatography (HPLC) using C_{18} reversed phase chromatography (mobile phase; methanol:water:triethylamine; 50:50:0.1; v/v). Polar compounds such as the oxidizing agent and inorganic salts elute near the void volume and the trimethylstannyl precursor (calculated log P = 6.130) does not elute under these preparative conditions (the precursor elutes only when 100% methanol is used during the cleaning step at the end of the preparation). The [^{123}I]5-IA (calculated log P = 1.889) peak is collected, isolated by SPE, and formulated with dehydrated alcohol injection, USP, ascorbic acid, and 0.9% NaCl and filtered through a 0.2 μm sterile membrane filter into a sterile serum vial. Quality control testing includes strength by gamma assay, monitoring radiochemical purity, specific activity and identity (retention times compared to authentic [^{127}I]5-IA UV-standard) by HPLC, pH, visual inspection, pyrogenicity and sterility by compendial tests (USP XXIV 2000). All testing, including inoculation of the sterility samples, is completed before release for administration to human subjects or patients.

The specific activity of the I-123 product is too high to measure. Depending on the scale of the reaction, the limit of detection of the HPLC ultraviolet detector sets a lower limit for the specific activity on the order of 5,000–10,000 Ci/mmol. Based on experiments carried out with iododestannylation with much larger amounts of radioactivity (McBride et al 1991) the actual specific activity is estimated to be on the

order of 180,000–240,000 Ci/mmol. Thus, the carrier dose is probably less than 0.002 µg; however, we have estimated a more conservative amount based on the limit of detection of the system (see "*7. Quantitative Composition of* **Drug**," page 1).

b) tBOC-5-IA-SnMe$_3$ ((S)-N-t-butoxycarbonyl-3-(2-azetidinylmethoxy)-5-trimethylstannylpyridine)



Scheme II. Synthesis of tBOC-5-IA-SnMe$_3$ precursor

The stannyl precursor **6** is synthesized by palladium catalyzed hexamethylditin stannylation of bromopyridine **5** (Scheme II) based on a published procedure (Musachio et al 1999), substituting hexamethylditin for the hexabutyl reagent. The product is characterized by elemental analysis, high performance liquid chromatography (HPLC), and nuclear magnetic resonance spectroscopy and compared to the literature (Koren et al 1998).

10. Description of containers, closures and packaging materials

The final dosage form is supplied as a sterile solution in sterile borosilicate 10-20mL serum vials with 20 mm gray butyl stoppers and aluminum ring seals. The vial is contained within an outer lead shield ("pig") to protect from gamma radiation.

11. Labels and labeling

Precursor is stored in airtight, labeled vials in conformance with regulations. The final product container bears the following label:

[^{123}I]-5-IA

NIH

Sterile, apyrogenic solution for intravenous administration

Caution: New drug limited by federal law to investigational use only

Inactive ingredients: sodium chloride (0.9%), ethanol as solubilizer, ascorbic acid for pH control

Expires: 36h after calibration Half-life of ^{123}I is 13.2 h

Concentration_____mCi/mL

Activity_____mCi Volume_____mL

Calib. Date_9-25-02_ Time_____ Lot No_MIB020925_

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12. Preparation and quality control instructions

See attached batch record.

13. Specifications for approval or rejection

Test	Specification
Identity (HPLC)	Rr = 0.8–1.2 (page 17)
Radiochemical Purity	NLT 90 %
pH	4–7
Visual Inspection	To Pass Test
Preparation Records	Complete & Accurate
Label	Complete & Accurate
Sterility Test	
At Release:	On Test
At Test:	Sterile
Pyrogen Test (LAL)	NMT 5 eu/mL
Expiration Period	36 h after calibration

14. Special notations and precautions

None.

B. Preliminary Data

1. Process Validation

The procedures described in the master production and control record were applied to four preparations of [I-123]5-IA. On a scale of 50 mCi, the average labeling yield was 49.2 ± 10.3% (mean ± standard deviation) and the isolated radiochemical yield in the final dosage form was 25.1 ± 17.8% (Table 2). The product met QC specifications in all cases (Table 3).

Table 2. [I-123]5-IA Synthesis Process Results. All radioactivity measurements decay-corrected to common time of calibration (noon, day of synthesis)

Date	*Lot Number*	*Scale (Start mCi)*	*Labeling Yield (%)*	*Radiochemical Yield (%)*
8/28/02	MIB020828	50.2	35.5	17.6
9/04/02	MIB020904	52.9	50.8	8.7
9/11/02	MIB020911	54.6	49.7	23.8
9/19/02	MIB020919	56.7	60.6	50.1
	mean	53.6	49.2	25.1
	±SD	±2.7	±10.3	±17.8
	n	4	4	4
	%CV	5.1	21.0	71.1
	min	50.2	35.5	8.7
	max	56.7	60.6	50.1
	median	53.8	50.3	20.7
	±SEM	±9.8	±4.0	±7.1

Table 3. [I-123]5-IA QC Results.

Date	*Lot Number*	*Strength (mCi)*	*Final Volume (mL)*	*HPLC Rt (min)*	*Identity (Rr)*	*Purity (%)*	*pH*	*Sterility, VI* [a]	*Pyrogens (eu/mL)*[e]
8/28/02	MIB020828	1.8	8.0	10.3[d]	1.0	97.2	7.0	Sterile	<5
9/04/02	MIB020904	5.0	8.8	9.3[d]	1.0	99.0	6.0	Sterile	<5
9/11/02	MIB020911	13.0	8.8	9.9[d]	1.0	95.5	6.0	Sterile	<5
9/19/02	MIB020919	28.4	9.4	10.0[d]	1.0	97.8	6.0	Sterile	<5
	mean	12.1	8.8	9.9	1.0	97.4	6.3		
	±SD	± 11.9	± 0.6	± 0.4	-	± 1.5	± 0.5		
	n	4	4	4	4	4	4		
	%CV	98.5%	6.6%	4.2%	-	1.5%	8.0%		
	min	1.8	8.0	9.3	1.0	95.5	6.0		
	max	28.4	9.4	10.3	1.0	99.0	7.0		
	median	9.0	8.8	9.95	1.0	97.5	6.0		
	±SEM	± 6.0	± 0.3	± 0.2	± 0.0	± 0.8	± 0.3		

Notes:

a All lots passed specifications for visual inspection.
b Not measured
c Performed on a “Luna” HPLC column
d Performed on a “Nova Pak” column
e eu = endotoxin units

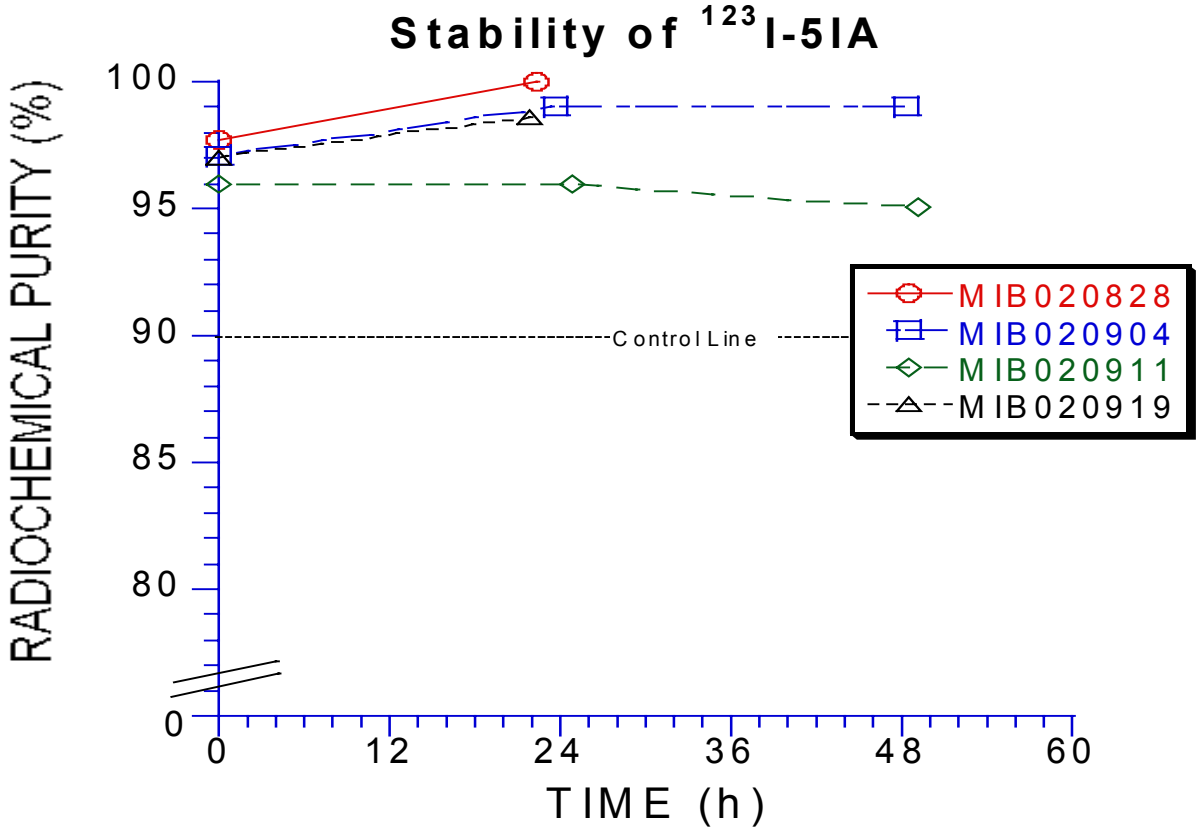

Figure 1. Stability of [I-123]5-IA stored in final dosage form in the sterile container-closure glass vial with 20 mm gray butyl stopper and aluminum seal at +4°C